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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants : Jaques Paris et al.

Serial No. : 09/423,109 Examiner: Sabiha Qazi

Filed : October 29, 1999 Art Unit: 1616

For : NEW HORMONAL COMPOSITION AND ITS USE

30 Rockefeller Plaza, 20th Floor
New York, New York 10112
December 4, 2009

Mail Stop RCE
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

RESPONSE TO DECEMBER 1, 2008 FINAL OFFICE ACTION, SUPPLEMENTAL INFORMATION DISCLOSURE STATEMENT AND PETITION FOR A FOUR-MONTH EXTENSION OF TIME AS A SUBMISSION ACCOMPANYING A REQUEST FOR CONTINUED EXAMINATION

A Notice of Appeal was filed in connection with the above-identified application, received by the U.S. Patent and Trademark Office on June 5, 2009. As a result an Appeal Brief was originally due August 5, 2009. Applicants hereby request a four-month extension of time, the fee for which is ONE THOUSAND SEVEN HUNDRED AND THIRTY DOLLARS ($1,730.00). A check for $2,540 is enclosed, which includes both the fee for a four-month extension of time and the $810.00 fee for filing a Request For Continued Examination. With a four-month extension of time the deadline for taking further action in connection with the subject application is December 5, 2009. Accordingly, this Response is being timely filed.

Remarks begin on page 2 of this paper.
A Supplemental Information Disclosure Statement begins on page 8 of this paper.

REMARKS

In the Final Office Action issued December 1, 2008 the Examiner rejected pending claims 3, 4, 7, 8, 18 and 31 and held claims 33-37 withdrawn from consideration as directed to a non-elected invention.

Priority

On page 3 of the December 1, 2008 Final Office Action the Examiner indicated that the specification should contain the priority data because "This application is 371 of PCT/FR99/02588 (10/25/1999)".

With respect, applicants note that this application is not a §371 national stage application. Although the application was originally filed as a §371 application the status of the subject application was changed to a §111 application as indicated in the December 7, 2004 Decision in response to applicants' Petition Under 37 C.F.R. §1.182, filed July 20, 2004.

Accordingly, applicants request that the Examiner reconsider and withdraw this ground of objection.

Information Disclosure Statement; Copending Application

On page 3 of the December 1, 2008 Final Office Action the Examiner referred to references needing to be submitted on PTO Form 892 (sic) and indicated that applicants must bring to the Examiner's attention copending applications which are material to the patentability of the claims pending in the subject application.

As pointed out in the Amendment mailed July 23, 2008 a detailed

Information Disclosure Statement was mailed to the U.S. Patent Office as part of the Amendment submitted on September 17, 2007 and a Supplemental Information Disclosure Statement was mailed January 23, 2008. To date, applicants have only received initialed copies of the PTO-1449 forms submitted with the September 17, 2007 Amendment.

Applicants note that a Supplemental Information Disclosure Statement was mailed January 23, 2008 to the U.S. Patent and Trademark Office in connection with the subject application. However, due to a typographical error, the Serial Number was incorrectly identified as U.S. Serial No. 09/432,109 on the January 23, 2008 Supplemental IDS. Applicants are submitting a Supplemental Information Disclosure Statement, which begins on page 8 of this paper, which includes the information provided in the Supplemental IDS filed January 23, 2008 and also includes additional references not included in the January 23, 2008 Supplemental IDS. Applicants note that the references listed in the subject specification are included in the Supplemental IDS which begins on page 8 of this paper.

Double Patenting Rejection

On pages 4-6 of the December 1, 2008 Final Office Action the Examiner rejected claims 3, 4, 7, 8, 18 and 31 on the ground of obviousness-type double patenting over claims 1-6 of U.S. Patent 6,831,073.

Applicants' claimed invention is based on the unexpected discovery that a lower progestative dose may be used to induce endometrium atrophy with good control of bleeding. Specifically, the recited 0.625 to 1.25 mg range of nomegestrol acetate per daily dose, is unobvious over claims 1-6 of U.S. Patent No. 6,831,073 because the claimed dose yields an unexpected result, namely, the surprising decoupling of the anti-estrogenic effect of nomegestrol acetate from

its progestational effect, when nomegestrol acetate is administered continuously in combination with an estradiol. As indicated on page 22 of the specification, the highest percentage of atrophic endometria was found at the lowest progestative dose. Thus, the results obtained with the claimed invention are unexpected.

One skilled in the art would have expected that low doses of nomegestrol acetate which are insufficient to induce secretory transformation of the endometrium would also be insufficient to preventing growth of the uterine muscosa and keep it in an atrophic condition. However, unexpectedly, nomegestrol acetate within applicants' claimed range when administered with an estradiol is sufficient to prevent growth of the uterine mucosa and to keep it in an atrophic condition.

Moreover, claims 1-6 of U.S. 6,831,073 provide methods for treating estrogenic deficiencies in post menopausal women, while applicants' claimed invention provides for method of treating a menopausal woman.

In view of the preceding remarks, applicants maintain that applicants' claimed invention is unobvious over claims 1-6 of U.S. Patent No. 6,831,073, and respectfully request that the Examiner reconsider and withdraw the rejection based on nonstatutory obviousness-type double patenting.

Rejections Under 35 U.S.C. §103

Applicants' claimed invention provides the following:

> Claim 18: A method of treating a menopausal woman comprising continuously orally administering without interruption to such menopausal woman a composition containing 0.5

to 1.5 mg of free estradiol or 1.5 to 2 mg of an estradiol ester, and from 0.625 to 1.25 mg of nomegestrol acetate per daily dose. [Emphasis added]

Claim 31: A pharmaceutical composition in oral administrable form comprising, in combination, from 0.5 to 1.5 mg of free estradiol or 1.5 to 3 mg of an esterified estradiol and from 0.625 to 1.25 mg of nomegestrol acetate. [Emphasis added]

Applicants' claimed invention is based on the surprising and unexpected discovery that a daily dose of 0.625 to 1.25 mg nomegestrol acetate can be used, in combination with 0.5 to 1.5 mg of free estradiol or 1.5 to 2 mg estradiol ester, as hormone replacement therapy to treat a menopausal woman so as to induce endometrium atrophy, i.e. to prevent growth of uterine mucosa, without inducing bleeding.

Applicants' claimed invention is further based on the surprising and unexpected discovery that when a daily dose of 0.625 to 1.25 mg nomegestrol acetate is administered, in combination with specific amounts of free estradiol or estradiol acetate, the anti-estrogenic effect of nomegestrol acetate can be decoupled from the progestational effect.

1. Rejection Under 35 U.S.C. §103 over Jamin in view of Martindale, Bazin et al., Paris et al. and Hodgen

As noted above, applicants' claimed invention relates to hormone replacement therapy in a menopausal woman. It is unrelated to contraception for a woman undergoing a normal menstrual cycle, i.e. a woman who is not menopausal.

Therefore, applicants do not understand the relevance of the cited references which concern contraception in non-menopausal women and are confused by the Examiner's discussion of the obviousness of using applicants' claimed dosage regimen for contraception. Clearly, there is no motivation to use a contraception regimen for hormone replacement therapy.

Moreover, none of the references cited in this ground of rejection disclose applicants' claimed dosage of 0.625 to 1.25 mg of nomegestrol acetate. Moreover, applicants' claimed dosage is neither contained within, nor overlaps with, the dosage of nomegestrol acetate disclosed in the cited references. Accordingly, there is no basis for a prima facie case of obviousness. (See the Examiner's Statement at the top of Page 12 of the December 1, 2008 Final Office Action and the cases cited there by the Examiner).

Finally, as noted above, applicants' claimed invention provides unexpected advantages and results which could not have been predicted from the cited references.

In view of the preceding remarks applicants request that the Examiner reconsider and withdraw the rejection of claims 3, 4, 7, 8, 18 and 31 over Jamin in view of Martindale, Bazin et al., Paris et al., and Hodgen.

2. Rejection Under 35 U.S.C. §103 Over Plunkett et al. and Blanc et al.

As acknowledged by the Examiner, Plunkett et al. do not disclose use of nomegestrol acetate at all, let alone use of 0.625 to 1.25 mg

nomegestrol acetate per daily dose.

Blanc et al. disclose use of a dose of nomegestrol of 2.5 mg/day, not the 0.625 to 1.25 mg range presently claimed. (Applicants note that the Examiner has incorrectly stated on page 19 of the December 1, 2008 Final Office Action that a lower limit of 0.3 mg nomegestrol acetate is presently claimed.)

Blanc et al. further disclose an estradiol dose of 2mg versus the currently claimed dose of 0.5 to 1.5mg of free estradiol. (Applicants note that the Examiner has incorrectly stated on page 19 of the December 1, 2008 Final Office Action that 0.3 to 3mg of estradiol is claimed).

Thus, applicants' claimed method involves a dose range of nomegestrol acetate and a dose range of free estradiol, neither of which dose ranges are included within, or overlap with, the ranges disclosed in the cited references. Accordingly, there is not a prima facie case of obviousness. (Once again, see the Examiner's comments at the top of page 12 of the December 1, 2008 Final Office Action the cases cited there by the Examiner.)

Moreover, as noted above, applicants' claimed invention provides unexpected advantages and results which could not have been predicted from the cited references.

In view of the preceding remarks applicants request that the Examiner reconsider and withdraw the rejection of claims 3, 4, 7, 8, 18 and 31 over Plunkett et al. and Blanc et al.

SUPPLEMENTAL INFORMATION DISCLOSURE STATEMENT

In accordance with their duty of disclosure under 37 C.F.R. §1.56, applicants direct the Examiner's attention to the following documents listed below which are also listed on Substitute Form PTO-1449 **(Exhibit A)**.

This Supplemental Information Disclosure Statement is being submitted pursuant to 37 C.F.R. §1.97(b)(4) before the mailing of a first Office action after the filing of a request for continued examination under §1.114. Thus, this Supplemental Information Disclosure Statement should be entered and considered.

In accordance with 37 C.F.R. §1.98(a)(2)(ii), copies of the U.S. Patents listed herein are not provided. Accordingly, copies of documents listed below as items 1-10 are not submitted herewith. Copies of documents listed below as items 11-88 are attached hereto as **Exhibits 1-78**.

1. U.S. Patent No. 4,820,831, issued April 11, 1989 for Ogata et al.;

2. U.S. Patent No. 5,108,995, issued April 28, 1992 for Robert F. Casper;

3. U.S. Patent No. 5,256,421 issued October 26, 1993 for Robert F. Casper;

4. U.S. Patent No. 5,585,370 issued December 17, 1996 for Robert F. Casper;

5. U.S. Patent No. 5,382,573 issued January 17, 1995 for Robert F.

Casper;

6. U.S. Patent No. 4,826,831 issued May 2, 1989 for Earl. R. Plunkett;

7. U.S. Patent No. 5,208,225 issued May 4, 1993 for Roger M. Boissonneault;

8. U.S. Patent No. 5,552,394 issued September 3, 1996 for Gary D. Hodgen;

9. Re-issue Patent No. Re 36,247 issued July 6, 1999 for Earl E. Plunkett et al.;

10. U.S. Patent Application Publication No. US 2007/0281912 A1 published December 6, 2007 for Jaques Paris;

11. European Patent No. 0 136 011 B1, granted January 22, 1997 **(Exhibit 1)**;

12. European Patent Application Publication No 0 309 263 A1, published March 29, 1989 **(Exhibit 2)**;

13. French Patent Application Publication No. 2,737,411, published February 7, 1997 **(Exhibit 3)**;

14. French Patent Application Publication No. 2,754,179, published April 10, 1998 **(Exhibit 4)**;

15. AFFINITO et al., (1998). "*Ultrasonographic Measurement Of Endometrial Thickness During Hormonal Replacement Therapy In Postmenopausal Women.*" Ultrasound Obstet Gynecol, 11:343-346

(Exhibit 5);

16. BASDEVANT et al., (1991). "*Effects Of Nomegestrol Acetate (5mg/D) On Hormonal, Metabolic And Hemostatic Parameters In Premenopausal Woman. Contraception*", 44(6):599-605 **(Exhibit 6)**;

17. BERNARD A.M. et al., (1994). "*Menopausal: Bone And Therapeutic Regimens (Cont)*" International Journal Of Gynecology & Obstetrics, Pp. 124 **(Exhibit 7)**;

18. BIRKAUSER M. et al. (1995). "*Substitution Hormonale: Une Indication Bien Posee Et Des Schemas, De Traitement Individuels Sont Determinants Pour Le Succes Du Traitement*" Med Et Hyg, 53:1770-3 **(Exhibit 8)**;

19. BOCANERA R. et al., (1993). "*Effect Of A HRT Regime (Micronized 17-Estradiol And Medroxy Progesterone Acetate) On The Endometria And Bleeding Pattern Of Climacteric Women. Bleeding And Endometrial Function*", P.17, Abstract No. 40 **(Exhibit 9)**;

20. CARRANZA-LIRA, (1998). "*Endometrial Changes According To Hormone Replacement Therapy Schedule*", Menopause: The Journal Of The North American Menopause Society, 5(2):86-89 **(Exhibit 10)**;

21. DOREN et al., (1996). "*Long-Term Compliance Of Continuous Combined Estrogen And Progestogen Replacement In Postmenopausal Women*", Journal Of The Climacteric & Postmenopause, 25:99-105 **(Exhibit 11)**;

22. DOREN et al., (1997). "*Uterine Perfusion And Endometrial Thickness In Postmenopausal Women On Long-Term Continuous Combined Estrogen And Progestogen Replacement*", Ultrasound

Obstet. Gynecol., 9:113-119 **(Exhibit 12)**;

23. DOREN & SCHEIDER, (1996). "*The Impacts Of Different HRT Regimens On Compliance*", Int. J. Fertil., 41(1):29-39 **(Exhibit 13)**;

24. DRAPIER FAURE E. (1992). "*Le Traitement De La Menopause Evitant Les Regles: Est-Il Possible?*" Est-Il Souhaitable? Gynecologie, 43(4-5):271-280, Including English Summary At P.271 **(Exhibit 14)**;

25. EIKEN et al., (1996). "*Effects Of 10 Years' Hormone Replacement Therapy On Bone Mineral Content In Postmenopausal Women*", Bone, 19(5):191S-193S **(Exhibit 15)**;

26. EIKEN et al., (1997). "*Effect On Bone Mass After Eight Years Of Hormonal Replacement Therapy*", British Journal Of Obstetrics And Gynaecology, 104:702-707 **(Exhibit 16)**;

27. EIKEN AND KOLTHOFF, (1995). "*Compliance With Long-Term Oral Hormonal Replacement Therapy*", Maturitas, 22:97-103 **(Exhibit 17)**;

28. ETTINGER et al., (1998). "*Comparison Of Continuation Of Postmenopausal Hormone Replacement Therapy: Transdermal Versus Oral Estrogen*", Menopause: The Journal Of The North American Menopause Society, 5(3):152-156 **(Exhibit 18)**;

29. FOX H. et al., (1993). "*Six Months Endometrial Histology Data On Continuous Estradiol Combined With 4 Different Dosages Of Continuous Dydrogesterone In More Than 300 Postmenopausal Women. Bleeding And Endometrial Function*", P.40, Abstract 119 **(Exhibit 19)**;

30. Hargrove J.T. Et Al., (1989). "*Menopausal Hormone Replacement*

Therapy With Continuous Daily Oral Micronized Estradiol And Progesterone", Obstetrics & Gynecology, 73:606-612 **(Exhibit 20)**;

31. HART et al., (1998). *"Long-Term Effects Of Continuous Combined HRT On Bone Turnover And Lipid Metabolism In Postmenopausal Women"*, Osteoporosis Int., 8:326-332 **(Exhibit 21)**;

32. KUHL, (1996). *"Comparative Pharmacology Of Newer Progestogens"*, Drugs, 51(2):188-215 **(Exhibit 22)**;

33. MIZANUMA et al., (1997). *"Prevention Of Postmenopausal Bone Loss With Minimal Uterine Bleeding Using Low Dose Continuous Estrogen/Progestin Therapy: A 2 Year Prospective Study"*, Maturitas, 27:69-76 **(Exhibit 23)**;

34. NEUMANN, (1977). *"Probleme Der Dosisfindung:Sexualhormone"*. Drug Res., Pp. 296-318, Including English Summary At P.296 **(Exhibit 24)**;

35. OETTEL et al., (1999). *"The Preclinical And Clinical Profile Of Dienogest: A Short Overview"*, Drugs Of Today, 35:3-12 **(Exhibit 25)**;

36. PATERSON et al., (1980). *"Endometrial Disease After Treatment With Oestergens And Progestogens In The Climacteric"*, British Medical Journal, Pp. 822-824 **(Exhibit 26)**;

37. PIEGSA et al., (1997). *"Endometrial Status In Post-Menopausal Woman On Long-Term Continuous Combined Hormone Replacement Therapy (Kliofem) A Comparative Study Of Endometrial Biopsy, Outpatient Hysteroscopy And Transvaginal Ultrasound"*, European Journal Of Obstetrics & Gynecology, 72:175-180 **(Exhibit 27)**;

38. RAUCH AND TAUBERT, (1993). "*Continuous Hormone Replacement Therapy With Estradiol Valerate And Chlormadinone Acetate In Adjectable Dosages*", Maturitas, 17:123-127 **(Exhibit 28)**;

39. RECKER et al., (1999). "*The Effect Of Low-Dose Continuous Estrogen And Progesterine Therapy With Calcium And Vitamin D Bone In Elderly Women*", Ann Intern Med., 130:897-904 **(Exhibit 29)**;

40. REUBINOFF et al., (1995). "*Effects Of Hormone Replacement Therapy On Weight, Body, Composition, Fat Distribution, And Food Intake In Early Postmenopausal Women: A Prospective Study*", Fertility And Sterility, 64(5):963-968 **(Exhibit 30)**;

41. STADBERG et al., (1996). "*17B-Estradiol And Norethisterone Acetate In Low Doses As Continuous Combined Hormone Replacement Therapy*", Maturitas, 23:31-39 **(Exhibit 31)**;

42. THOMAS et al., (1993). "*Postmenopausal Hormone Therapy*", 7th Intern. Cong. On The Menopause, Stockholm, Abstract No. 372 **(Exhibit 32)**;

43. ULRICH et al., (1997). "*Quality Of Life And Patient Preference For Sequential Versus Continuous Combined HRT: The UK Kliofem Multicenter Study Experience*", International Journal Of Gynecology & Obstetrics, 59:S11-S17 **(Exhibit 33)**;

44. WHITEHEAD et al., (1982). "*Effects Of Various Types And Dosages Of Progestogens On The Postmenopausal Endometrium*", The Journal Of Reproductive Medicine, 27(8):539-548 **(Exhibit 34)**;

45. WOLFE AND PLUNKETT, (1994). "*Early Effects Of Continuous Low-*

Dosage Dl-Norgestrel Administered Alone Or With Estrogen", Maturitas, 18:207-219 **(Exhibit 35)**;

46. WOLFE AND HUFF, (1995). *"Effects On Continuous Low-Dosage Hormonal Replacement Therapy On Lipoprotein Metabolism In Postmenopausal Women"*, Metabolism, 44(3):410-417 **(Exhibit 36)**;

47. BERGINK, et al. (1981) *"Effect Of Oestriol, Oestradiol Valerate And Ethinyloestradiol On Serum Proteins In Oestrogen-Deficient Women,"* Maturitas, 3 (3-4) : 241-247 **(Exhibit 37)**;

48. BERNARD A. M. et al., (1994), *Menopausal: Bone and Therapeutic Regimens (Cont)*. International Journal of Gynecology & Obstetrics, pp. 124 **(Exhibit 38)**;

49. BOTELLA et al. *"Regulation Of Rat Uterine Steroid Receptors By Nomegestrol Acetate, A New 19-Nor-Progesterone Derivative"* Abstract of J. Pharmacol. Exp. Ther. 1989, Feb; 248(2): 758-61 **(Exhibit 39)**;

50. BOTELLA et al. *"Kinetic Analysis Of The Binding Of Nomegestrol Acetate To The Progesterone Receptors In Rat Uterus By Competition Studies"* Fundam. Clin. Pharmacol. 1990; 4(5): 511-23 **(Exhibit 40)**;

51. BOTELLA et al. *"Lack Of Estrogenic Potential Of Progesterone- Or 17-Norprogesterone-Derived Progestins As Opposed To Testosterone Or 19-Nortestosterone Derivatives On Endometrial Ishikawa Cells"* J. Steroid. Biochem. Mol. Biol. 1995, Oct; 55(1): 77-84 **(Exhibit 41)**;

52. COHEN et al. "*Traitement Des Femmes En Périménopause Par 5 Mg/J D'acétate De Nomégestrol, 20 Jours Par Cycle*" Contracept. Fertil. Sex. (1992) - Vol. 20, n° 11, 1054-1057, including an English language abstract **(Exhibit 42)**;

53. CONRAD et al. "*Cardiovascular Risk Factors and Combined Estrogen-Progestin Replacement Therapu: A Placebo-Controlled Study With Noegestrol Acetate and Estradiol*", Fertility and Sterility, Vol. 64, No. 5, 1995, pp. 957-962 **(Exhibit 43)**;

54. COUZINET et al. "*The Antigonadotropic Activity Of Progestins (19-Norprogesterone And 19-Norprogesterone Derivatives) Is Not Mediated Through The Androgen Receptor*" J. Clin. Endocrinol. Metab. 1996, Dec; 4218-4223 **(Exhibit 44)**;

55. COUZINET B., et al. *(1999) "The Antigonadotropic Activity Of A 19-Nor-Progesterone Derivative Is Exerted Both At The Hypothalamic And Pituitary Levels In Women,"* The Journal of Clinical Endocrinology & Metabolism, vol.84, n°11, pp.4191-4196 **(Exhibit 45)**;

56. DESREUX et al. "*Effects Of A Progestogen On Normal Human Breast Epithelial Apoptosis On Vitro And In Vivo*" The Breast (2003), 12, 142-149 **(Exhibit 46)**;

57. DORANGEON et al. "*Effects Of Nomegestrol Acetate On Carbohydrate Metabolism*" Diabete & Metabolisme (paris) (1993), 19, 441-445 **(Exhibit 47)**;

58. DORANGEON et al. "*Short Term Effects On Lipids And Lipoproteins Of Two Progestogens Used In Postmenopausal Replacement Therapy*" European Journal of Clinical Research (1992), 3: 187-193 **(Exhibit**

48);

59. DORANGEON et al. "*Traitement De L'endométriose Par L'acétate De Nomégestrol*" Gynécologie, 1993, 1, 3, 139-143, including an English language abstract **(Exhibit 49);**

60. DUC at al. "*Antiandrogenic Properties Of Nomegestrol Acetate*" Arzneim. Forsch. Drug/Res. 1995, 45(1): 70-74 **(Exhibit 50);**

61. DUC et al. "*Interaction Of [3H] Nomegestrol Acetate With Cytosolic Progesterone Receptors From The Rat Uterus*" Steroids, 1991, Jun; 56(6): 325-328 **(Exhibit 51);**

62. FOIDART et al. "*Impact Of Percutaneous Oestradiol Gels In Postmenopausal Hormone Replacement Therapy On Clinical Symtoms And Endometrium*" British Journal of Obstetrics and Gynaecology March (1997), Vol. 104, 305-310 **(Exhibit 52);**

63. LINDBERG et al. *(1989) "A Comparison Between Effects Of Estradiol Valerate And Low Dose Ethinyl Estradiol On Haemostasis Parameters"* Thrombosis & Haemostasis, 61(1), pp.65-9 **(Exhibit 53);**

64. NGUYEN -PASCAL et al. *"Nomegestrol Acetate May Enhance The Skeletal Effects Of Estradiol On Biochemical Markers Of Bone Turnover In Menopausal Women After 12-Week Treatment Period"* Climacteric 2005; 8: 136-145 **(Exhibit 54);**

65. PARIS, et al. (1983), *"The Pharmacological Profile of TX 066 (17alpha-acetoxy-6-methyl-19-nor-4,6-pregnadiene-3,20-dione), a New Oral Progestative"*. Arzneimittelforschung, Vol. 33, No. 5, pp. 710-715 **(Exhibit 55);**

66. PARIS, et al. *(1987) "Extinction Of Mineralocorticoid Effects In 19-Norprogesterone Derivatives: Structure-Activity Relationships,"* The Journal of Pharmacology and Experimental Therapeutics, vol.243, n°1, pp.288-291 **(Exhibit 56)**;

67. POWERS et al., *"Pharmacokinetics and Pharmacodynamics Of Transdermal Dosage Forms of 17beta-estradiol: Comparison With Conventional Oral Estrogens Used For Hormone Replacement"*, Am. J. Obstet. Gynecol. (1985), Vol. 152, No. 8, pp.1099-1106 **(Exhibit 57)**;

68. REYONLDS, J. *"MARTINDALE, The Extra Pharmacopoeia - Sex Hormone"* 30th Edition Pharmaceutical Press (1993), pp. 1166-1198 **(Exhibit 58)**;

69. Suplemento afna No. 1, Mayo 1991, Seccion II 57 **(Exhibit 59)**;

70. THOMAS J. L., et al. *"Les Progestatifs - Effets Biologiques Et Implications Thérapeutiques"* Revue française d'Endocrinologie, Nutition et Métabolisme, (1986), 27, n° 4-5, 389-403, including an English translation **(Exhibit 60)**;

71. TIMMER et al. *"Bioequivalence Assessment Of Three Different Estradiol Formulations In Postmenopausal Women In An Open, Randomized, Single-Dose, 3-Way Cross-Over Study"* Europ.J.Drug.Metab.& Pharmaco., 1999, vol.24, n°1, pp.47-53 **(Exhibit 61)**;

72. VON SCHOULTZ, et al. *(1989) "Estrogen Therapy And Liver Function-Metabolic Effects Of Oral And Parenteral Administration,"* Prostate, 14 (4), pp.389-395 **(Exhibit 62)**;

73. WILLIAMS et al., (Nov. 1998) *"Coadministration Of Nomegestrol Acetate Does Not Diminish The Beneficial Effects Of Estradiol On Coronary Artery Dilator Responses In Nonhuman Primates (Macaca fascicularis)"* Am. J. Obstet. Gynecol. Vol 179(5), pp.1288-1294 **(Exhibit 63)**;

74. ZARTARIAN et al. (1998) *"Effets Sur La Qualités Des Cycles Et Les Bouffées De Chaleur Du Nomégestrol Acétate Administré Seul Ou Associé En Séquentiel Inversé Au 17 Bêta Estradiol Cutané Chez Des Femmes En Périménopause"* Contracept. Fertil. Sex. Vol 26 (1), pp. 69-76, including an English language abstract **(Exhibit 64)**;

75. ZARTARIAN et al. (1998) *"Tolérance Biologique Et Clinique Du Nomégestrol Acétate, Administré Seul Puis Associé En Séquentiel Inversé Au 17 Bêta Estradiol Cutané, Chez Des Femmes À Risques Présentant Une Dyslipoprotéinémie De Type IIa"* Annales d'endicrinologie (Paris), 59, 411-416, including an English language abstract **(Exhibit 65)**;

76. European Patent Application Publication No. EP 0,235,090 A1, published September 2, 1987 for Boissenault **(Exhibit 66)**;

77. European Patent Application Publication No. EP 0,253,607 A1, published January 20, 1998 for Upton et al **(Exhibit 67)**;

78. European Patent Application Publication No. EP 0,491,415 A1 published June 24, 1992 for Bergink **(Exhibit 68)**;

79. European Patent EP 1 227 814 B1 granted January 5, 2005 **(Exhibit 69)**;

80. United Kingdom Patent Application Publication GB 2 216 420 published October 11, 1989 **(Exhibit 70)**;

81. PCT International Application Publication No. WO 96/09826 published April 4, 1996 for Schering Aktiengesellschaft **(Exhibit 71)**;

82. PCT International Application Publication No. WO 96/10991 published April 18, 1996 for Astra Aktiebolag Friess **(Exhibit 72)**;

83. PCT International Application Publication No. WO 97/04784 published February 13, 1997 for Laboratoire Theramex, including an English language abstract **(Exhibit 73)**;

84. PCT International Application Publication No. WO 98/15279 published April 16, 1998 for Laboratoire Theramex, including an English language abstract **(Exhibit 74)**;

85. PCT International Application Publication No. WO 01/30355 A1 published May 3, 2001 for Laboratoire Theramex, including an English language abstract **(Exhibit 75)**;

86. PCT International Application Publication No. WO 01/30358 A1 published May 3, 2001 for Laboratoire Theramex, including an English language abstract **(Exhibit 76)**;

87. BARRET-CONNOR et al., (1989) "*Estrogen Replacement and Corony Heart Disease*" Cardiovascular clin., vol. 19, n°3, pp. 159-172 **(Exhibit 77)**; and

88. ZIMMERMAN et al., (1999) "*Pharmacokinetics Of Dienogest As A Single Drug Or In Combination With Estradiol Valerate Or Ethinylestradiol,*" Drugs Of Today, 35, pp.27-39 (**Exhibit 78**).

The Examiner is respectfully requested to make these reference of record in the present application by initialing and returning a copy of the enclosed substitute Form PTO 1449.

Conclusion

For the reasons set forth on pages 2-7 of this paper, applicants maintain that the grounds of the Examiner's rejections have been overcome and respectfully request that the Examiner reconsider and withdraw these grounds of rejections and allow the pending claims.

If a telephone interview would be of assistance in advancing prosecution of the subject application, applicants' undersigned attorney invites the Examiner to telephone him at the number provided below.

No fees, other than the enclosed $1,730.00 fee for a four-month extension of time and $810.00 fee for filing a Request For Continued Examination (RCE), are deemed necessary in connection with the filing of this Response, Supplemental Information Disclosure Statement and the accompanying RCE. Accordingly a check in the amount of $2,540.00 is enclosed. However, if any additional fee is required, authorization is hereby given to charge the amount of such fee to Deposit Account No. 03-3125.

Respectfully submitted,

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